CASE REPORT

Psychiatry and Clinical Psychopharmacology 2021;31(2):238-240
10.5152/pcp.2021.21101

Psychotic Agitation in a Patient with COVID-19: Pathogenesis or Iatrogenesis?

Umit Haluk Yesilkaya, Yasin Hasan Balcioglu, Meltem Sen

Department of Psychiatry, Bakirkoy Prof Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, Istanbul, Turkey

ABSTRACT

The pathophysiological underpinnings of central nervous system (CNS) involvement in SARS-CoV-2 infection, as well as the profile of adverse neuropsychiatric effects of pharmacological agents employed in the management of COVID-19, are yet to be elucidated. Here, we report a 43-year-old female patient who suffered from COVID-19 and who developed new-onset psychotic agitated behavior which may be related to either the COVID-19 infection itself or to the drugs that were used in the treatment. On her third day of treatment with oseltamivir, hydroxychloroquine, and azithromycin, the patient, who had no previous background of neurological or psychiatric diagnosis, presented with a new-onset psychomotor agitation with auditory hallucinations and insomnia. Her psychiatric symptoms have improved with oral olanzapine 5 mg/d. This report underscores the importance of neuropsychiatric monitoring in patients with COVID-19. Clinicians should be aware of the limited knowledge on the neuropsychiatric safety profile of the medication used for COVID-19 treatment, while they have focused on the neuropsychiatric outcomes of COVID-19 itself.

ARTICLE HISTORY

Received: 6 January, 2021
Accepted: 14 February, 2021

KEYWORDS: Coronavirus pandemic, COVID-19, neuropsychiatric symptoms, psychosis, SARS-CoV-2, side effects, viral encephalitis

INTRODUCTION

There have already been reports of patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection with associated neuropsychiatric manifestations, although the virus primarily affects the respiratory system.[1] Cases of febrile seizures, convulsions, changes in mental state, and encephalitis have been reported due to both SARS-CoV-2 and other human coronaviruses.[2,3] However, pathophysiological underpinnings of central nervous system (CNS) involvement in SARS-CoV-2 infection are yet to be elucidated. Recent publications have postulated several theories that neuropsychiatric manifestations related SARS-CoV-2 infection might be associated with the involvement of both direct viral transmission and neuroimmune response in the brain.[1,4] Although in some latest reports, neuropsychiatric side effects such as psychotic symptoms and agitation associated with oseltamivir and hydroxychloroquine were noticed,[4,5] the neuropsychiatric adverse-effect profile of pharmacological agents including oseltamivir, hydroxychloroquine, and azithromycin which are employed in the management of Coronavirus Disease-2019 (COVID-19) still needs to be disclosed. Here, we report a COVID-19 patient who developed new-onset psychotic agitated behavior which may be related to either the COVID-19 infection itself or to its management with oseltamivir, hydroxychloroquine, and azithromycin.

CASE PRESENTATION

A 43-year-old female patient was admitted to the emergency department with complaints of chills, fatigue, and cough for the past three days. Body temperature was 38°C. Blood tests, computed tomography (CT) of the chest, and real time-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 were performed. Blood screening results at admission showed an increased level of C-reactive protein (CRP) (34 mg/dL) and decreased lymphocyte count of (0,78 L × 103/μL), while white blood cell count (WBC), thyroid, liver, and renal functions, creatine kinase (CK), ferritin, D-Dimer, and electrolytes were in the normal range. Her CT scan of the chest showing ground-glass opacities revealed coherence with COVID-19 infection, while the patient was confirmed to be COVID-19 positive based on the RT-PCR test result. Hydroxychloroquine at 400 mg/day, azithromycin 200 mg/day, and oseltamivir 75 mg/day, all of which are included in the current national protocol for the treatment of COVID-19, were orally administered. On

Corresponding author: Yasin Hasan Balcioglu, E-mail: yhasanbalcioglu@gmail.com

Cite this article as: Yesilkaya U, Balcioglu Y, Sen M. Psychotic agitation in a patient with COVID-19: Pathogenesis or iatrogenesis?. *Psychiatr and Clin Psychopharmacol*. 2021; 31(2): 238-240.

her third day of the treatment, she presented with a new-onset psychomotor agitation, manifested as screaming, physically aggressive behavior at home, auditory hallucinations (talking to herself in her room while alone), and insomnia, despite having had no previous background of a neurological or psychiatric diagnosis and no history of alcohol or substance abuse. The examination of her mental state revealed the following: cooperation and orientation were intact, while output and speed of speech, as well as psychomotor activity, were increased. The patient was anxious, while her mood was dysphoric. She was talking to herself during the examination, which was suggestive of auditory hallucinations. The scale for the assessment of the positive symptoms (SAPS) score was 62. The results of blood screening showed that while CRP (24mg/dL) was high, other parameters were normal, based on which we ruled out metabolic and endocrine conditions that might explain such a clinical presentation. After a detailed neurologic examination, we recorded the findings as follows: cranial nerves were intact, psychomotor agitation existed but neither neuromuscular nor basal ganglia abnormality was identified. According to the patient's history and electroencephalogram findings, epilepsy was excluded. Cranial magnetic resonance imaging did not show any diffusion restriction or structural pathology. Orally administered olanzapine at 5 mg/day was added to the ongoing treatment, for the management of psychiatric symptoms. At the fifth day of olanzapine treatment, hallucinations and agitated behavior were improved (SAPS:16). Following completion of the 14-day treatment regime for COVID-19 infection, an RT-PCR test confirmed a negative SARS-CoV-2 infection, while auditory hallucinations completely resolved after three days of completion of the COVID-19 treatment. On her routine psychiatric evaluation 15 days after discharge, she declared that she was not able to remember the initiation of the psychiatric symptoms. Detailed examination at the follow-up revealed no significant psychopathologic, neurologic, or abnormal physical finding, while the SAPS score was 2. Olanzapine was continued for a month for maintenance and gradually stopped afterward.

DISCUSSION

Despite the considerable recognition of the neuroinvasive potential and neurodegenerative effects of the SARS-CoV-2 infection obtained from both early data of COVID-19 research and clinical studies of previous coronavirus outbreaks including SARS and Middle East respiratory syndrome (MERS),[3] the underlying pathophysiologic processes of the neuropsychiatric outcomes of SARS-CoV-2 infection itself and those of the neuropsychiatric adverse effects of the drugs used in the management of COVID-19 still need to be elucidated. SARS-CoV-2 may infect peripheral immune cells and may lead to a process resulting in neurodegeneration by penetrating the blood–brain barrier through the infected immune cells, consequently perpetuating neuroinflammation.[3,4] Moreover, it has been suggested that individuals with increased plasma antibody levels as a result of coronavirus immunoreactivity are more prone to develop psychiatric complications.[6] In addition, SARS-CoV-2 may attach to not only peripheral cells but also the cells in the CNS. Since SARS-CoV-2 binds to angiotensin-converting enzyme-2 (ACE-2) receptors located on glial and neuronal cell membranes, such a binding may trigger an inflammatory response in the CNS through increasing ACE-2-associated TNF-alpha, IL-1, and IL-6 release,[1,7] which might be associated with neuropsychiatric manifestations including psychotic agitation and affective symptoms.[8] Alternatively, SARS-CoV-2 may infiltrate the CNS via either hematogenous transmission or retrograde axonal transport from peripheral nerves; and infiltration of the virus itself may play a role in neuronal death, which may lead to neuropsychiatric manifestations.[9]

On the other hand, we have considered that the acute psychotic symptoms and agitated behavior of our patient might be related to the medication used in COVID-19 treatment. Previous studies have suggested that oseltamivir, a viral neuraminidase inhibitor, may act as either a monoamine oxidase inhibitor or a monoaminergic modulator and may induce psychotic symptoms.[10,11] In addition, hydroxychloroquine, another agent used in COVID-19, has been reported to induce several psychiatric adverse effects, including positive psychotic symptoms, that may be associated with the inhibitory effect of hydroxychloroquine on acetylcholinesterase, leading to a cholinergic imbalance.[5,12] Unlike oseltamivir and hydroxychloroquine, azithromycin seems less likely to be associated with neuropsychiatric presentations, according to the current line of scientific evidence.

Cerebrospinal fluid (CSF) examination has been frequently reported negative in such acute neuropsychiatric manifestations.[13] This indicates that the initial clinical approach in such circumstances should consider existing causative factors that are potentially related to the presenting symptoms.[14] Despite the presumption that the psychiatric symptoms of our patient are related to the infection, medication or both, the absence of a CSF examination should be considered as a limitation in explaining precise etiology. Clinicians may undervalue the adverse effects of medications while they have focused on the neuropsychiatric outcomes of COVID-19 itself. Therefore, it should be considered that, in addition to the CNS involvement of SARS-CoV-2 infection, the neuropsychiatric safety profile of the medication used for the treatment has yet to be clarified.

Informed Consent: Informed consent was obtained from the participant who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – U.H.Y., M.S;Design - U.H.Y., M.S.; Supervision - Y.H.B.; Resource - U.H.Y.; Materials - U.H.Y.; Data Collection and/or Processing - U.H.Y., M.S.; Analysis and/or Interpretation - U.H.Y., Y.H.B.; Literature Search - M.S.; Writing - U.H.Y., Y.H.B.; Critical Reviews - Y.H.B.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received the unconditional support of Abdi Ibrahim Ilac Sanayi ve Tic. A.S. for the purpose of scientific contribution. All opinions and claims within this work belong to the authors themselves, and cannot be associated to Abdi Ibrahim.

REFERENCES

1. Troyer EA, Kohn JN, Hong S. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain Behav Immun*. 2020;87:34-39. [CrossRef]
2. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091. [CrossRef]
3. Desforges M, Le Coupanec A, Dubeau P, et al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses*. 2019;12(1):14. [CrossRef]
4. Yesilkaya UH, Balcioglu YH. Neuroimmune correlates of the nervous system involvement of COVID-19: a commentary. *J Clin Neurosci*. 2020;78:449-450. [CrossRef]
5. Hiasa M, Isoda Y, Kishimoto Y, et al. Inhibition of MAO-A and stimulation of behavioural activities in mice by the inactive prodrug form of the anti-influenza agent oseltamivir. *Br J Pharmacol*. 2013;169(1):115-129. [CrossRef]
6. Mascolo A, Berrino PM, Gareri P, et al. Neuropsychiatric clinical manifestations in elderly patients treated with hydroxychloroquine: a review article. *Inflammopharmacology*. 2018;26(5):1141-1149. [CrossRef]
7. Severance EG, Dickerson FB, Viscidi RP, et al. Coronavirus immunoreactivity in individuals with a recent onset of psychotic symptoms. *Schizophr Bull*. 2011;37(1):101-107. [CrossRef]
8. Yesilkaya UH, Balcioglu YH, Sahin S. Reissuing the sigma receptors for SARS-CoV-2. *J Clin Neurosci*. 2020;80;72-73. [CrossRef]
9. McKernan DP, Dennison U, Gaszner G, Cryan JF, Dinan TG. Enhanced peripheral toll-like receptor responses in psychosis: further evidence of a pro-inflammatory phenotype. *Transl Psychiatry*. 2011;1(8):e36-e36. [CrossRef]
10. Balcioglu YH, Yesilkaya UH, Gokcay H, Kirlioglu SS. May the central nervous system be fogged by the cytokine storm in COVID-19?: an appraisal. *J Neuroimmune Pharmacol*. 2020;15(3):343-344. [CrossRef]
11. Hiasa M, Isoda Y, Kishimoto Y, et al. Inhibition of MAO-A and stimulation of behavioural activities in mice by the inactive prodrug form of the anti-influenza agent oseltamivir. *Br J Pharmacol*. 2013;169(1):115-129. [CrossRef]
12. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet*. 2015;385(9979):1729-1737. [CrossRef]
13. O'Shaughnessy TJ, Zim B, Ma W, et al. Acute neuropharmacologic action of chloroquine on cortical neurons in vitro. *Brain Res*. 2003;959(2):280-286. [CrossRef]
14. Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. *Clin Infect Dis*. 2013;57(8):1114-1128. [CrossRef]